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10/813,097	03/30/2004	Choong-Chin Liew	4231/2055K	5239

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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/813,097	LIEW, CHOONG-CHIN	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of Group I, further electing the marker CDC14A in the reply filed on 3/12/07 is acknowledged. Claims 49-57 are pending and examined in this office action.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 51-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation "unfractionated samples of lysed blood" in claim 51 is unclear in light of the prosecution history in this application and in the parent applications from which this application claims priority. Claims 52-57 depend from claim 51 and are indefinite for this same recitation. The specification does not define what is meant by an "unfractionated samples of lysed blood." On its face, such a limitation appears to mean that the whole blood sample is not separated into constituent parts, however, interpretation of the claim in light of the specification, pending claims, and applicant's remarks filed with the amendment results in ambiguity with regard to the meaning of this claim limitation.

An example in the specification which discusses lysis prior to quantification includes a centrifugation step after which the "pellet" is further treated. This is a fractionation after lysis but before quantification.

One might interpret detecting in "unfractionated sample of lysed blood" as requiring that the detection occur relative to RNA that was extracted from the entire blood sample without any prior separation into parts, which could be accomplished by direct extraction of the whole blood without separating removing the plasma from the blood sample, for example.

Applicant set forth still a different definition for a similar claim limitation in the remarks filed introducing a similar phrase into the claims in the parent application 10/268730. In discussing basis in the specification for the limitation, applicant stated that the limitation refers to "a sample of whole blood which has not been fractionated into cell populations and includes a drop of blood (see remarks dated 4/25/05, at page 5)." This definition for unfractionated sample of whole blood set forth by applicant would, therefore, allow a fractionation of the cellular material prior to RNA extraction (as exemplified in the instant specification in Example 5).

And so it is unclear what the metes and bounds of the phrase "unfractionated sample of lysed blood" actually encompasses in light of the lack of definition of the phrase in the specification and the many, conflicting possible interpretations in light of the specification, pending claims, and remarks by applicant.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 51-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The limitation "unfractionated samples of lysed blood" appears to be new matter. The amendment which added this limitation did not cite support for the limitation. The specification teaches at page 43 treating a sample with lysing buffer, centrifuging the sample, and then processing the pellet with RT-PCR (Example 5). Thus, the sample was fractionated prior to quantifying. The examiner was not able to identify basis for this limitation in the specification.

6. Claims 49-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention

The invention is drawn to a method detecting Chagas' disease in a human test subject. The claims all include a step of determining the level RNA encoded by the gene BTG family, member2 (CDC14A) in a blood sample obtained from said human and comparing the level with the level of control RNA encoded by said gene in RNA of blood samples from control subjects, and wherein said comparison is indicative of Chagas' disease in said human test subject. Thus, the independent claim, as written, states that a comparison of a human test subject CDC14A RNA level in a blood sample to a control indicates that Chagas' disease is present in the test subject. The nature of the invention requires the knowledge of a reliable association between

comparing CDC14A expression and the indication that Chagas' disease is present in a human. Further, the practice of the invention requires an understanding of how the presence of Chagas' disease effects the level of CDC14A expression in human blood in patients having Chagas' disease versus patients that do not have Chagas' disease but may have some other disorders.

Scope of the claims

The claims are extremely broad because they require set forth that any or all comparison between a test subject and RNA level from "control subjects" is indicative of disease. The claims are broad with regard to whether or not the comparison requires identifying a difference in expression or not, and if a difference is detected whether that is an increase in RNA levels or a decrease in RNA levels. The claims are broad with regard to the "control subjects" would could encompass patients with Chagas' disease, healthy patients, patients with some other disease, such as depression or rheumatoid arthritis or multiple sclerosis, and set forth that the comparison alone is sufficient to indicate Chagas' disease, no matter the result of the comparison. Later claims further define the control subject and require a statistically significant difference or similarity in RNA levels between control subjects and test subject, but even these claims do not set forth the direction of the difference necessary to indicate Chagas' disease. The claims are very broad in scope because they encompass that ANY level and direction of difference in gene expression between the tested subjects is indicative of disease. That is, the claims do not set forth that one level should be higher or lower than the other, and further do not set forth how much of a "difference" between two individuals would be necessary to draw the conclusions set forth in the claims.

Teachings in the Specification/Examples

Regarding Chagas' disease, the specification provides example 28 wherein gene expression profiles of blood samples from individuals having Chagas' disease were compared with normal individuals, that is healthy patients. The specification teaches that 668 genes were identified as being differentially expressed between patients having symptomatic and asymptomatic Chagas disease versus healthy patients, and regarding the instant claims, table 3Y provides a list of these genes (Example 28). CDC14A is among the genes.

Table 3Z teaches that the ratio of expression in Chagas disease samples relative to control samples is 1.47 for asymptomatic patients and 1.95 for symptomatic patients, indicating that in the tested samples, CDC14A was expressed, on average at a 1.47 or 1.95 times higher level in Chagas disease patients versus healthy controls. Table 3Y teaches that the result is significant for all Chagas disease patients combined p=0.0492.

The claims suggest that detecting and comparing expression of CDC14A in a test patient versus any possible set of control patients alone is sufficient to indicate the presence of Chagas' disease (that is detect Chagas' disease). The plain language of the claims suggests that any comparison between a test subject and control subjects, even as few as two control subjects, is sufficient to conclude that Chagas' disease is detected.

The specification does not provide data to support the breadth of assertion in the claims- namely that comparison of the CDC14A expression level in a test sample to control subjects (any control subjects) is sufficient to detect Chagas' disease in a test patient. Claim 54 is limited to a case where the control subjects do not have Chagas' disease, but they could still have any other possible disease or condition. For example, the claims are inclusive of control subjects that have other disorders of the cardiovascular system or other systemic diseases.

Furthermore, though the specification teaches that this gene is differentially expressed in Chagas' disease patients versus healthy patients, the specification teaches this is true for hundreds of genes. There is no guidance or analysis of data in the specification to suggest that this gene in particular is sufficient to conclude that Chagas' disease is present in a sample, as is instantly claimed. This information is essential to understanding and practicing the claimed invention because it is critical to knowing how to interpret a particular comparison result.

State of the Prior Art and Level of Unpredictability

The expression of genes in example 21 was tested by hybridization of samples to a microarray that contains genetic information for tens of thousands of genes. This technology area is highly unpredictable, and as a result significant guidance is required to practice inventions using this type of data. Lee (Clinical Chemistry, 47:8, 1350-1352 (2001)) teaches that despite the technical accuracy of individual observations on an array, these data "are much more prone to numerous false-positive findings fundamentally because of (a) an extremely large number of observations and (b) a very wide dynamic range of gene expression values obtained from gene chip experiments." In view of these unpredictable aspects of applying such data, Lee teaches that replication is necessary to begin to screen out false positive results. There is no replication in the instant specification.

Observing differences in expression between two populations is a highly unpredictable endeavor. While the instant specification teaches that CDC14A is differentially expressed in a population of Chagas' disease patients versus control subjects, the specification does not establish that any particular level of expression of CDC14A (relative level or raw level) is

sufficient to DETECT Chagas' disease to the exclusion of other disorders, which is encompassed by the instant claims, and indeed, suggested by the instant claims.

Showe et al. (US 2006/0271309) teach that CDC14A is differentially expressed in blood of patients with cutaneous T-cell lymphoma versus a group of controls that included healthy patients (See examples, Tables 1). This disease are very different from Chagas' disease, yet it displays a similar expression phenotype- that is differential expression of CDC14A in blood samples from patients with illness versus healthy controls. This exemplifies that it is highly unpredictable whether or not one can conclude, simply from a blood sample of a test patient, that Chagas' disease is present, since increased expression of the gene in blood could indicate some other disorder or phenotype is present, whether that cutaneous T-cell lymphoma or some other disease which has not yet been analyzed.

Tsuang et al. undertake an analysis that is very similar to the one in the instant specification, albeit with a different disease as the subject of the study. Regarding their results, Tsuang et al. caution that the results must be interpreted with caution given several limitations including small sample size, the fact that the findings are not replicated in a separate cohort and results "may represent chance findings and type-I inferential errors," and that the patients tested were all on drugs that were not accounted for in the analysis (American Journal of Medical Genetics, Part B (Neuropsychiatric Genetics) 133B:1-5(2005)). All of these cautions set forth by Tsuang et al. appear to be equally relevant to the study set forth in the instant application. All of these taken together underscore and highlight the very unpredictable nature of this technology area.

Furthermore, although CDC14A was not observed to be differentially expressed in any of the other examples in this specification, it is unknown and unpredictable whether it would be expressed in the blood of patients having other cardiac illnesses or any other diseases which were not tested in the instant specification or diseases which were tested in the instant specification but in a different population of test subjects, and whether this expression would be different from levels of expression in healthy controls. A method for detection which relies on a comparison between expression in the blood of a test subject and control subjects requires the knowledge of this information in order to reliably "detect" Chagas' disease, as set forth in the claims. The instant specification has not established that all difference, no matter the magnitude nor the direction, relative to any control subjects or even relative to a healthy control subject is indicative of Chagas' disease. Furthermore, the specification has not shown that all expression at a level statistically the same as that observed in a population of patients having Chagas' disease is sufficient to conclude that Chagas' disease is present, as set forth in claim 55. In fact, as previously noted, Showe et al. observed that this gene is differentially expressed in a disease with highly dissimilar etiology. It is entirely unpredictable if this is also the case with other diseases. It is not known under what circumstances the result observed in the instantly examined control and test populations would be repeatable, as the results have not been validated. All of these inquiries are particularly important in this case since the claims are silent as to which differential expression observations would be sufficient to detect the presence of Chagas' disease.

Further, the claims of the instant application set forth the comparison of the gene expression in a single individual versus as few as two other individuals, and they set forth that a

comparing gene expression between the two is "indicative of" Chagas' disease. Neither the specification nor the claims set forth a threshold of difference between an individual's expression and the control expression of CDC14A in the blood that would be sufficient to conclude that the difference in gene expression between a test individual and any type control group is "indicative of" the recited Chagas' disease. Because the claims encompass any level of altered gene expression, it is relevant to point out that the art of Cheung et al (2003) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) (p.422, last paragraph; Fig 1). The data indicates that, for example, expression of ACTG2 in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3). It is thus unpredictable as to whether or not any level of altered gene expression is indicative of a Chagas' disease or the absence of Chagas' disease.

The unpredictability of correlating gene expression level to any phenotypic quality is taught in the post-filing art of Wu (2001). Wu teaches that gene expression data, such as microarray data, must be interpreted in the context of other biological knowledge, involving various types of 'post genomics' informatics, including gene networks, gene pathways, and gene ontologies (p.53, left col.). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as

normalization and such basic assumptions as normality (p.63 - Discussion). The art of Newton et al (2001) further teaches the difficulty in applying gene expression results. Newton et al. teaches that a basic statistical problem is determining when the measured differential expression is likely to reflect a real biological shift in gene expression, and replication of data is critical to validation (p.38, third full paragraph). There is no replication of data in the instant specification.

Quantity of Experimentation

The instant specification does not provide enabling support for the practice of a single embodiment within the claimed invention since the claimed invention results in the detection of Chagas' disease. In particular, the specification does not provide adequate guidance to appraise one of ordinary skill in the art as to what levels of CDC14A gene expression must be observed to successfully conclude that Chagas' disease is present. Further, although the specification teaches there are differences in CDC14A levels in a Chagas' disease population versus a control patient population, and the specification teaches that for this population the difference is a 1.47 or 1.95 fold increase, the specification does not support the assertion in the claims that observing such an increase relative to any and all control populations of 2 or more individual is sufficient to "detect" Chagas' disease. Thus, given the lack of teaching in the specification and the highly unpredictable nature of the technology, an extensive amount of work would be required to practice the claimed invention.

In order to practice the claimed invention, one would have to undertake an extensive amount of experimentation in a highly unpredictable technology area. One would have to begin by validating the results observed in the instant specification in a separate population of healthy and Chagas disease patients, in view of the established level of unpredictability in this

technology area. One would have to further complete similar analysis for other diseases and conditions and control populations versus healthy controls and versus Chagas disease controls in order to attempt to establish when and if analysis of CDC14A expression alone is sufficient to conclusively detect Chagas' disease, as set forth in the claims. How different from the average level of expression of healthy individuals would the test result have to be to indicate Chagas' disease? Would any difference, up or down regulation be indicative of Chagas' disease? Or could one result indicate Chagas' disease and one a different disease such as CTCL or other diseases of the heart? Is CDC14A expressed in the blood of individuals with a disease other than Chagas' disease and CTCL relative to healthy individuals? Is this expression also diagnostic of other disorders entirely unrelated to Chagas' disease? In order to reliably use a method for detecting Chagas' disease, one would first have to answer at least these questions. One would also, however, have to carry out this testing for validation, for it is possible that the result observed in the instant specification is intrinsic to the cohort of patients evaluated in applicant's study. Further, one would have to undertake experimentation to determine difference thresholds required to determine that a patient has or does not have a disease.

As discussed, this art area is highly unpredictable.

Conclusion

The claims include methods which encompass the detection in blood of the expression of CDC14A in a test subject and comparing this expression to control subjects, wherein the comparison itself "is indicative of Chagas' disease." The identification of gene differential expression/disease indication relationships is a highly unpredictable endeavor, requiring extensive experimentation. The specification provides minimal guidance. In light of the factors

discussed, therefore, it is concluded that it would require undue experimentation to practice the claimed invention.

Conclusion

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Thursday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Juliet C. Switzer
Primary Examiner
Art Unit 1634

May 29, 2007